Complete Summary

GUIDELINE TITLE

Antithrombotic therapy supplement.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Aug. 64 p. [118 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Apr. 49 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Conditions that require anticoagulation therapy (e.g., thrombosis)
- Conditions that may result from anticoagulation therapy (e.g., bleeding)

GUIDELINE CATEGORY

Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Neurology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide a resource for the clinician in the use of antithrombotic drugs
- To help physicians make risk-benefit treatment decisions
- To serve as a tool to use for patients treated with anticoagulants

- To bring about consistency in recommendations that are common to the scope of related Institute for Clinical Systems Improvement (ICSI) cardiovascular guidelines: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis.

TARGET POPULATION

Any patient receiving anticoagulation therapy

Note: Refer to related National Guideline Clearinghouse (NGC) summaries of the Institute for Clinical Systems Improvement (ICSI) cardiovascular guidelines for specific target populations: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Risk assessment (risk of thrombosis if untreated versus risk of bleeding if treated)
2. Pre-treatment assessment, including complete blood count (CBC), platelet count, prothrombin time (PT), international normalized ratios (INRs), activated partial thromboplastin time (aPTT), creatine, liver enzymes, and albumin
3. Anticoagulants
    - Warfarin
    - Unfractionated heparin (UFH)
    - Low-molecular-weight heparin (LMWH)
    - Synthetic pentasaccharide (fondaparinux)
    - Alternative agents in selected cases: such as direct thrombin inhibitors, antiplatelet agents (oral and parenteral)
4. Reversal of anticoagulation
    - Vitamin K
    - Fresh frozen plasma (FFP)
    - Protamine sulfate
5. Patient education
6. Monitoring of anticoagulation therapy by establishing INRs or by using aPTTs or heparin assays or by performing periodic platelet counts
7. Perioperative management including:
    - Bridging therapy (e.g., taking a patient off warfarin in the perioperative setting and "bridging" with heparin)
    - Management of neuraxial blockade

MAJOR OUTCOMES CONSIDERED

Safety and Efficacy of Anticoagulation

- Risk and incidence of adverse effects of anticoagulation, (e.g., major bleeding, skin necrosis, heparin induced thrombocytopenia)
- Therapeutic anticoagulation levels (e.g., international normalized ratio [INR])

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search of clinical trials, meta-analysis, and systematic reviews is performed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

New Guideline Development Process

A new guideline, order set, and protocol is developed by a 6- to 12-member work group that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, along with an Institute for Clinical Systems Improvement (ICSI) staff facilitator. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 members may be recruited from medical groups or hospitals outside of ICSI.

The work group will meet for seven to eight three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and footnotes and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Critical Review Process

Every newly developed guideline or a guideline with significant change is sent to Institute for Clinical Systems Improvement (ICSI) members for Critical Review. The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the ICSI.

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Approval

Each guideline, order set, and protocol is approved by the appropriate steering committee. There is one steering committee each for Respiratory, Cardiovascular, OB/GYN, and Preventive Services. The Committee for Evidence-based Practice approves guidelines, order sets, and protocols not associated with a particular category. The steering committees review and approve each guideline based on the following:

- Member comments have been addressed reasonably.
- There is consensus among all ICSI member organizations on the content of the document.
- Within the knowledge of the reviewer, the scientific recommendations within the document are current.
- Either a critical review has been carried out, or to the extent of the knowledge of the reviewer, the changes proposed are sufficiently familiar and sufficiently agreed upon by the users that a new round of critical review is not needed.

Once the guideline, order set, or protocol has been approved, it is posted on the ICSI Web site and released to members for use. Guidelines, order sets, and protocols are reviewed regularly and revised, if warranted.

Document Revision Process

ICSI scientific documents are revised every 12 – 36 months as indicated by changes in clinical practice and literature. Every 6 months, ICSI checks with the work group to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Prior to the work group convening to revise the document, ICSI members are asked to review the document and submit comments. During revision, a literature search of clinical trials, meta-analysis, and systematic reviews is performed and reviewed by the work group. The work group will meet for 1-2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

If there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations, it is sent to members to review prior to going to the appropriate steering committee for approval.

Review and Comment Process:

ICSI members are asked to review and submit comments for every guideline, order set, and protocol prior to the work group convening to revise the document.

The purpose of the Review and Comment process is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the order set and protocol. Review and Comment also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes needed across systems in their organization to implement the guideline.

All member organizations are encouraged to provide feedback on order sets and protocol, however responding to Review and Comment is not a criterion for continued membership within ICSI.

After the Review and Comment period, the work group reconvenes to review the comments and make changes as appropriate. The work group prepares a written response to all comments.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guidance, refer to "Summary of Changes Report -- August - 2007."

These recommendations supplement the recommendations on anticoagulation therapy provided in the National Guideline Clearinghouse (NGC) summaries of the Institute for Clinical Systems Improvement (ICSI) guidelines: Atrial Fibrillation; Heart Failure in Adults; Diagnosis and Initial Treatment of Ischemic Stroke; Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS); Venous Thromboembolism, and Venous Thromboembolism Prophylaxis.

Class of evidence (A-D, M, R, X) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights

- There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy. Clinicians must consider the risks and benefits of anticoagulation therapy for a patient based upon the individual's risk for thrombosis if not treated weighed against the risk of bleeding if treated. (*Introduction, Annotations #2, 3, 4, 12, 13, 14, 15, 26, 27, 29, 36, 37, 39, 46, 47, 49, 55, 56, 58*)
- In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate-acting anticoagulant agents (unfractionated heparin [UFH]/low-molecular-weight heparin [LMWH]/fondaparinux) should be used concomitant with warfarin. (*Annotation #7*)
- Loading doses and rapid induction of warfarin should be avoided. (*Annotation #7*)
- Many prescription medications or over-the-counter remedies, including dietary supplements and herbs, may alter the effectiveness of anticoagulants (detected by the international normalized ratio [INR]) and/or reduce the effectiveness of platelets (not detected by the INR). (*Annotations #7; see also Annotations Appendices B, C, D in the original guideline document*)
- Vitamin K may be used to reverse supratherapeutic anticoagulation with warfarin. The dose of vitamin K depends upon the degree of INR elevation and/or signs and symptoms of bleeding. Vitamin K can lead to warfarin resistance and subsequently to an increased risk of thromboembolism. (*Annotation #9*)
- Regardless of the anticoagulant used, it is important that patients know they must always inform their physician and other health care providers that they are on anticoagulation therapy, especially if they are undergoing an invasive procedure. (*Annotations #10, 20, 24, 34, 44, 54, 63; see also Appendix D in the original guideline document*)
- Patients should be encouraged and empowered to play an active role in the self-management of their treatment. Self-management is best initiated and sustained through active involvement of patients and family members with their multidisciplinary health care team. This educational partnership should be encouraged to decrease potential risks and improve understanding of the importance of patient adherence to their treatment regimen. (*Annotation #10, 20, 24, 34, 44, 54, 63; see also Appendix D in the original guideline document*)
- Patients with mechanical heart valves and who are pregnant have complex anticoagulation needs and should be managed by an anticoagulation expert. (*Annotations #4,15*)

Warfarin

1. **Introduction**

   Warfarin is used in the chronic management of patients with several types of thrombotic diseases. It produces its anticoagulant effect by inhibiting the vitamin K dependent production of clotting factors II, VII, IX, and X, and proteins C and S. Warfarin is not fully effective in the initial several days of therapy because of a delayed reduction in some of the clotting factors that it inhibits. In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate acting anticoagulant agents (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, direct thrombin inhibitors [DTIs]) should be used concomitantly with warfarin.

   When determining the efficacy and tolerability of warfarin in patients with non-valvular atrial fibrillation, the clinical trials excluded patients using the following criteria:

   Table 1: Exclusion Criteria Used in Trials Evaluating the Efficacy and Tolerability of Anticoagulation in Patients with Non-valvular Atrial Fibrillation

Active bleeding
Active peptic ulcer disease
Known coagulation defects
Thrombocytopenia (platelet less than 50,000/mm^3) or platelet dysfunction
Recent hemorrhagic stroke
Noncompliant or unreliable patients
Patient is psychologically or socially unsuitable
Dementia or severe cognitive impairment
History of falls (three within the previous year or recurrent, injurious falls)
Excessive alcohol intake
Uncontrolled hypertension (greater than 180/100 mm Hg)
Daily use of nonsteroidal anti-inflammatory drugs (NSAIDs)
Planned invasive procedure or major surgery

   The clinician will need to balance the potential increased risk in bleeding against the potential decreased risk of thromboembolism when evaluating warfarin therapy.

   Evidence supporting this recommendation is of class: R

2. **Contraindications**

   Key Points:

   - All contraindications are relative to a patient's risk for thrombosis weighed against their risk for bleeding while on anticoagulation therapy.

Warfarin Allergy or Intolerance

Acute rash, hepatitis, diarrhea, or nausea may indicate an allergy or intolerance to warfarin.

Hemorrhage

Anticoagulation with warfarin is contraindicated in patients with active hemorrhage with possible exceptions in certain circumstances such as disseminated intravascular coagulation as a result of malignancy. The decision to initiate anticoagulation should be individualized for patients with a history of recent hemorrhage. Again, this is dependent on circumstances including the type of hemorrhage and the indication for anticoagulation. Withholding anticoagulation for four to six weeks may be prudent for non-central nervous system bleeds. This duration may be longer for central nervous system (CNS) bleeds and needs to be assessed on a case-by case basis.

See Appendix A, "Risk Factors for Bleeding During Warfarin Therapy" in the original guideline document and Annotation #3, "Adverse Effects" for additional information about predicting the risk of bleeding for individual patients.

Pregnancy

See Annotation #4, "Pregnancy - Contraindicated."

3. **Adverse Effects**

Key Points:

- The most common adverse effect of warfarin is bleeding. Risk factors for bleeding include patient-related and treatment-related factors.

Bleeding

Patients treated with usual doses of warfarin have a 2-4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage. Risk factors for bleeding include patient-related factors and treatment-related factors.

Patient-related factors include age, previous episodes of bleeding, anemia (hematocrit [HCT] less than 30%), hypertension, heart disease, cerebrovascular disease, renal disease, history of gastrointestinal (GI) hemorrhage, active peptic ulcer disease or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant falls, regular use of NSAIDs, and use of other medications or natural remedies.

The U.S. Food and Drug Administration (FDA) recently approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35-50% of the

variable dose response to warfarin. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs.

While there is clinical evidence that the presence of these genetic variations may impact the choice of the initial warfarin dose, there are no trials, at present, that have shown using genetic testing will have an impact on short- and long-term safety and patient outcomes. The FDA has not made the testing for the two gene variations mandatory.

The work group feels that more clinical trials are necessary before recommending routine testing of patients for these genetic variations. There are many other variables that influence a patient's response to warfarin therapy. Most important is that all patients initiating warfarin need frequent, careful monitoring to assess their response to this therapy.

Advanced patient age and hypertension are two predictors of risk strongly related to the inherent risk of intracerebral hemorrhage in patients not receiving anticoagulation. Combined literature sources support age as a risk for intracerebral hemorrhage that increases by 1.85/year/decade, with particular caution above 75 years of age.

Treatment-related factors include duration, intensity, and variability of warfarin treatment, concomitant use of aspirin, and support patients receive from their providers and home environments. Please refer to Appendix A, "Risk Factors for Bleeding During Warfarin Therapy" in the original guideline document for additional information on bleeding risk in anticoagulation therapy.

Risk factors for bleeding should not be considered absolute contraindications to anticoagulant therapy. Some risk factors for bleeding (such as age) are also risk factors for thromboembolism. **The potential increased risk of bleeding must be balanced against the potential decreased risk of thromboembolism**.

Evidence supporting this recommendation is of classes: A, B, C, D, R

Skin Necrosis

Skin necrosis is a rare but serious complication of warfarin therapy that typically occurs on the third to eighth day of therapy. Warfarin should be discontinued in patients with evidence of skin necrosis.

When warfarin-induced skin necrosis is suspected, patients should be placed on heparin therapy unless there is evidence of heparin induced thrombocytopenia (HIT).

Evidence supporting this recommendation is of classes: D, R

Purple Toe Syndrome

Purple toe syndrome and other manifestations of peripheral emboli may rarely complicate warfarin therapy, usually 3 to 10 weeks after initiation of therapy. Causes of purple toe syndrome other than warfarin should be considered when making a treatment decision. These include vasculitis, acute myocardial infarction (MI) with embolism, and diabetes mellitus.

Evidence supporting this recommendation is of classes: D, R

Less Serious Adverse Effects

Adverse effects that are less serious include alopecia, osteoporosis, gastrointestinal discomfort, and rash. Management of these adverse effects should be managed on an individual basis.

Evidence supporting this recommendation is of classes: B, D

4. **Pregnancy - Contraindicated**

Warfarin is contraindicated during pregnancy because it crosses the placenta causing teratogenicity and fetal bleeding.

Unfractionated and low molecular weight heparins do not cross the placenta and do not cause teratogenicity or fetal bleeding. Therefore, UFH or a LMWH should be used in place of warfarin. A recent study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. **Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert**.

Evidence supporting this recommendation is of class: R

5. **Breast Feeding**

The amount of warfarin in breast milk is too small to affect the baby. As a result, breastfeeding is safe for mothers taking warfarin and for their infants.

6. **Monitoring**

Test

The INR is the preferred test for monitoring warfarin therapy.

The INR is calculated from the Prothrombin Time (PT) as follows:

$$(\text{Patient PT}/\text{Mean Normal PT})^{\text{ISI}}$$

The International Sensitivity Index (ISI) is a measure of sensitivity of the thromboplastin. The manufacturer provides this information. The laboratory instrumentation used for INR testing may cause a clinically significant change in the ISI.

Limitations of INR

There are several recognized limitations of the test, including instrumentation effect on the ISI and erroneous reporting of the ISI by the thromboplastin manufacturer.

Timing and Frequency of INR Testing

During initiation and maintenance therapy with warfarin, the INR is best measured at least 16 hours after the dose of warfarin.

INR determinations should be obtained monthly in most stable patients, and no more than six weeks should elapse between determinations.

Influence of Heparin and Lupus Anticoagulants on the INR

Prothrombin reagents contain a heparin neutralizer; however, presence of high concentrations of heparin in plasma samples (e.g., sample collected shortly after intravenous [IV] heparin bolus, or sample collected above an IV infusion of unfractionated heparin, or sample collected through a heparin-coated catheter [central venous line or arterial line]) will spuriously prolong the INR.

Prothrombin reagents contain a high concentration of phospholipids; thus, presence of lupus anticoagulants typically does not affect the INR result.

However, there are individual patients in whom lupus anticoagulants may spuriously prolong INR results obtained by some instrument-reagent combinations. In these patients, lupus anticoagulants can cause a prolongation of the PT and INR, resulting in a perceived overestimation of a patient's anticoagulation.

Alternatives to INR in Patients with Lupus Anticoagulants

For patients with a prolonged baseline PT/INR due to a lupus anticoagulant, alternatives to the INR have been evaluated. Measurement of chromogenic factor X levels or factor II levels may be helpful in the monitoring of warfarin therapy in selected patients with lupus anticoagulant. Both the chromogenic factor X and factor II levels may not be readily available.

Evidence supporting this recommendation is of classes: A, D, R

Blood Samples

Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma.

- The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient's hematocrit is greater than 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted.

- Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing.

Evidence supporting this recommendation is of classes: B, R

Refer to the original guideline document for information on instruments including point of care instruments and reagents.

7. **Dosing**

Key Points:

- Patients receiving warfarin for the first time should begin at the patient's estimated average daily dose (typically 5 mg/day; range 2.5 to 7.5 mg/day), with a recheck of INR in two to three doses.
- Steady-state INR values will not be realized for up to three weeks following a dose adjustment.

Testing must be completed and results reviewed before initiation of warfarin:

- Complete blood count (CBC)
- Platelet count
- PT/INR
- Activated partial thromboplastin time (aPTT)
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [GGT])
- Albumin

General Principles of Warfarin Dosing

Loading doses and rapid induction of warfarin should be avoided. Warfarin (irrespective of INR) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose.

See "Patient Related Factors" under Annotation #3"Adverse Effect" for a discussion of the updated labeling for warfarin.

Patients at high risk of thrombosis, such as those with an active thrombotic process (e.g., venous thromboembolism [VTE]) or an underlying malignancy, should be treated with concomitant immediate-acting anticoagulant (UFH, LMWH, fondaparinux, DTIs) and warfarin therapy. Patients at lower thrombotic risk (e.g., atrial fibrillation without recurrent thromboembolism) can be initiated on warfarin alone.

A single target INR value should be used as a goal endpoint. This will decrease the odds of a patient being above or below desirable range of INR. The target INR for most conditions is 2.5 with an acceptable range of 2.0 to 3.0. Other thrombotic conditions (e.g., mitral mechanical valves) have recommended targets of 3.0 (range 2.5 to 3.5). A table of recommended therapeutic ranges for oral anticoagulant therapy is available in Annotation #8, "Recommended Therapeutic Range for Oral Anticoagulation Therapy" in the original guideline document. Also, individual disease management guidelines such as Atrial Fibrillation and Venous Thromboembolism give specific INR recommendations.

The risk of bleeding for patients on warfarin increases substantially at INR values greater than 4.0. This risk is magnified if one or more risk factors are present. Consider hemorrhagic risk in all dosing decisions. Please refer to Appendix A, "Risk Factors for Bleeding During Warfarin Therapy," of the original guideline document for more information on risk factors for bleeding during warfarin therapy.

There is a significant increase in thromboembolism as INR values decrease below INR 1.7. Clinical risk and past medical history should be considered in all dosing decisions. Higher risk may require more aggressive dosing.

In most cases, holding warfarin for 4 days prior to surgery results in an INR value of 1.2 or less. Expect advanced age and drug interactions to result in a slower decline. Patients with high risk of thromboembolism may need coverage with heparin for a portion of this time. For more information, see Annotation #65, "Anticoagulation Bridging."

Some equivalency studies have shown that substitution of generic warfarin for brand name Coumadin® may provide equivalent anticoagulation response if the manufacturer of the generic warfarin has followed the standards set for the name brand. Care must be taken to remain with either the brand name product or the same generic product. Do not switch from brand to generic or between generics.

Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Dietary supplements including herbal or natural remedies can change the INR response to warfarin and/or increase a patient's risk of bleeding. In these instances, additional monitoring may be needed. See Appendices B, "Drug Interactions with Warfarin" and C, "Endogenous Interactions with Warfarin" in the original guideline document for more information on drug interactions with warfarin.

Mechanism of drug-drug interactions occur commonly by the cytochrome P450 enzyme metabolizing system. Metabolism of the object or substrate medication may either be induced or inhibited by the interacting drug. Induction will result in a diminished pharmacodynamic response, while inhibition will result in an increased pharmacodynamic response.

Foods that contain moderate amounts of vitamin K may decrease the INR response to warfarin. Patients should be encouraged to not change their diet while taking warfarin and not change the amount of foods containing vitamin

K they normally eat each day. See Annotation #10, "Key Patient Education Components" for a guide to educating patients regarding warfarin therapy.

Direct thrombin inhibitors (hirudin, argatroban, bivalirudin) and heparins can affect the INR. See Annotations #35-44, "Direct Thrombin Inhibitors" for more information.

Evidence supporting this recommendation is of classes: A, B, D, R

Initiation of Warfarin

Average Daily Dosing Technique (for patients not on heparin)

Average daily dosing technique is useful for patients off UFH and LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients previously taking warfarin can be initiated at the previous dose.

Patients receiving warfarin for the first time should begin at an average dose of 5 mg daily with a recheck of INR in two to three doses. Lower initiation doses should be considered for patients with any of the following factors: age greater than 75 years, multiple comorbid conditions, poor nutrition (low albumin), elevated INR when off warfarin, elevated liver function tests, or changing thyroid status. For patients who weigh more than 80 kg, a higher estimated average initial dose of 7.5 mg may be given. Higher initial dosing nomograms have not shown consistent benefit. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose.

See "Patient Related Factors" under Annotation #3"Adverse Effect" for a discussion of the updated labeling for warfarin.

If the INR is 2.0 or greater after the first 3 doses, consider decreasing the dose by one-half. Always search for causes of rapid rise in INR such as poor nutritional status, infection, or systemic disease process. See Appendix C in the original guideline document for more information on endogenous interactions with warfarin.

Subsequent INR values are determined at two to three times weekly for one to two weeks, then less often depending on the stability of the INR result.

Steady state anticoagulation occurs between 6 to 12 days. Expect obese patients and patients of advanced age to take longer to reach steady state.

Evidence supporting this recommendation is of classes: A, B, D, R

Flexible Daily Dosing Technique (for patients on heparin)

The flexible daily dosing technique is useful for patients on concomitant UFH or a LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients are given daily doses of warfarin, adjusted according to the daily INR, until a weekly dose can be determined.

The dose-response relationship is best interpreted when there are at least 16 hours between dose and laboratory draw.

Evidence supporting this recommendation is of class: D

Maintenance Dosing of Warfarin

An assessment of clinical variables known to affect the INR (including a change of patient adherence, change of other medications [e.g., amiodarone], change of food or alcohol consumption, change of activity level) should be made with each dose adjustment. Always search for the cause of out-of-range values and address them before adjusting the dose.

Expect a 15% dose adjustment to result in an approximately 1.0 INR change. Likewise, a 10% dose adjustment will result in an approximate 0.7 to 0.8 INR change.

Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.

Patients with INR values by $\pm$ 0.5 INR out-of-range should be considered for more frequent monitoring and should have a repeat INR within seven days.

If two consecutive weekly INR values are within range and there has not been a change in clinical variables known to effect the INR, the interval between draws may be gradually increased to monthly, and not more than 6 weeks.

Options for Dosing and Management

Anticoagulation clinics have been shown to significantly reduce patients' risks of adverse events.

Though traditionally, warfarin has been monitored at a central laboratory and managed by the patient's physician, new monitoring and management options have emerged.

Anticoagulation clinics staffed by pharmacists/registered nurses (RNs) have been shown to significantly reduce patients' risks of adverse events.

Computer-assisted dosing has been slow to develop, but may someday improve the quality of anticoagulation adjustments and offer superior management for difficult or high-risk patients.

Selected point-of-care instruments have received FDA approval for patient self-testing.

While some patients may prefer self-management, clinical experience, reimbursement, and research are insufficient to support widespread implementation of patient self-management. Further research is needed to better identify appropriate candidates for self-management, and to delineate the key components of education and support.

Evidence supporting this recommendation is of classes: A, B, C, D, R

8. **Recommended Therapeutic Range for Oral Anticoagulation**

Recommended therapeutic range for oral anticoagulation therapy is provided in the original guideline document.

9. **Correction of Supratherapeutic Anticoagulation Caused by Warfarin**

Supratherapeutic anticoagulation may occur with patients taking warfarin. Vitamin K may be used to reverse the effects of warfarin; however, vitamin K can lead to warfarin resistance and, subsequently, to an increased risk of thromboembolism.

Evidence supporting this recommendation is of classes: A, B, C, D, R

Important Considerations for Vitamin K Dosing

In an outpatient clinic setting, oral vitamin K is the preferred route of administration.

In a hospital setting, when patients are ill or taking nothing by mouth, intravenous vitamin K may be the preferred route of administration. To avoid anaphylactic reactions, vitamin K should be given over 30 minutes in a mixture of dextrose 5% in water (D5W) 50 mL under monitored conditions. It is not necessary to premedicate with corticosteroids or antihistamines.

Administration of vitamin K by subcutaneous or intramuscular injections is not recommended due to unpredictable absorption which can lead to erratic correction of the INR and resistance to warfarin.

Refer to Table 2 in the original guideline document for details on correction of supratherapeutic warfarin anticoagulation caused by warfarin.

Evidence supporting this recommendation is of classes: B, C, R

10. **Key Patient Education Components**

Mechanism of action of warfarin: it depletes certain coagulation factor proteins in the blood.

Time of day to take warfarin: it should be taken at approximately the same time each day. Due to the short half-life of factor VII and its influence on the INR, this is especially important if the patient will have an INR drawn the next morning.

Explanation of INR, target range, and regular testing

Signs and symptoms of bleeding and that the provider should be contacted immediately if bleeding signs are present.

Need to notify provider if illness, injury, or change in physical status occurs.

Need to inform all their health care providers of anticoagulation therapy, especially if potentially undergoing an invasive procedure, surgery or dental work.

Drug interactions:

- What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin is unknown: check INR within three to four days.
- Drugs that affect the absorption of warfarin
- Drugs that increase or decrease the effect of warfarin
- Common over-the-counter medication interactions, including aspirin, NSAIDs, acetaminophen, natural or herbal remedies, laxatives, antacids, and multivitamin preparations containing vitamin K

Role of vitamin K and the importance of consistency of vitamin K rich foods in the diet rather than avoidance of vitamin K rich foods

Importance of minimizing trauma risk associated with activities at high risk for injury

Effect of exercise: increased activity results in decreased effect of the drug

Effect of personal habits: alcohol, chewing tobacco, etc.

Effect of certain conditions: congestive heart failure, thyroid disease, gastroenteritis, and diarrhea

Importance of self-monitoring: maintain a log of INRs, dose of warfarin, etc.

Medic Alert® bracelet/necklace and warfarin ID card.

See Appendix D in the original guideline for a guide to patient education regarding warfarin therapy.

Heparin (Unfractionated and Low-Molecular-Weight Heparin)

11. **Introduction**

Heparin's (UFH, LMWH) anticoagulant effect is due to the presence of a pentasaccharide sequence which potentiates the action of antithrombin III leading to inactivation of several clotting factors--primarily factors Xa and IIa.

Heparins have relatively rapid onset of action compared to warfarin and are often the first drug used in acute thrombotic situations.

UFH is derived from porcine or bovine sources. It has variable absorption, metabolism, and pharmacokinetics and effects on anticoagulation. Monitoring is required in most patients treated with this drug.

LMWH are depolymerized byproducts of UFH. Pharmacological advantages of LMWH relate to superior absorption and consistent dose effect response.

12. **Contraindications**

    Active major bleeding including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated

    Thrombolytics given within past 24 hours for acute stroke

    Hypersensitivity to heparin or pork products

    Heparin-induced thrombocytopenia (HIT)

    Renal failure (LMWH and fondaparinux)

13. **Precautions**

    Active or history of recent gastrointestinal ulceration and hemorrhage

    Bacterial endocarditis

    Bleeding diathesis

    Concomitant therapy with agents that inhibit platelets

    Congenital or acquired bleeding disorders

    Hemorrhagic stroke

    Status post brain, spinal, or ophthalmologic surgery

    Uncontrolled arterial hypertension

    Diabetic retinopathy

14. **Adverse Effects**

    Key Points:

    - Heparin-induced thrombocytopenia (HIT) should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a

greater than 50% decrease in platelet count from baseline labs while on heparin.
- All heparin should be stopped in patients suspected of having HIT until antibody test results are available.
- If the patient is on concomitant warfarin and HIT is suspected, the warfarin should be stopped, the warfarin effects corrected, and patient started on DTI therapy.

Bleeding

Risk of bleeding increases with treatment-related factors such as dose, duration, and use of thrombolytics and/or antiplatelet agents, and patient-related factors including age over 70 years, recent trauma or surgery, coagulopathy, peptic ulcer, neoplasm, or renal failure.

Evidence supporting this recommendation is of classes: A, R

Heparin-Induced Thrombocytopenia (HIT)

HIT is an immune-mediated reaction to heparins. It occurs in 2 to 3% of patients treated with UFH and less than 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH.

HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin.

Delayed-onset HIT is an increasingly recognized form of this disorder. Patients with delayed-onset HIT typically present with thromboembolic complications one to two weeks (range 5 to 40 days) after receiving their last dose of LMWH or UFH. They frequently display mild or moderate thrombocytopenia. When HIT is not recognized as the etiology of the thromboembolic complication, the patient is frequently rechallenged with heparin, causing significant worsening of the thrombosis, as well as the thrombocytopenia. These patients typically have very high titers of HIT-related antibodies. The possibility of delayed onset HIT should be considered in any patient presenting with thromboembolism after a recent hospitalization.

In vitro data have not demonstrated cross reactivity of fondaparinux with HIT antibodies. However, there is one report of HIT with fondaparinux.

Patients suspected of having any form of HIT should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for

patients with HIT. Three brands are FDA approved: argatroban, lepirudin (Refludan®), and most recently bivalirudin (Angiomax®).

If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped. The warfarin effect should be reversed with vitamin K and DTI therapy should be initiated. Low maintenance doses of warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a five-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes.

See Annotations #35--44, "Direct Thrombin Inhibitors" for more information.

Evidence supporting this recommendation is of class: R

15. **Pregnancy**

Adverse Effects in Pregnancy

UFH and LMWH do not cross the placenta and therefore do not cause teratogenicity or fetal bleeding, though bleeding at the uteroplacental junction is possible.

Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and the manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant. However, the available data sets, clinical trials, reviews, and registry data suggest that, compared with UFH, LMWHs may be safe and effective agents in pregnant women with mechanical heart valves.

The American College of Chest Physicians (ACCP) recommends that women requiring long-term anticoagulation with warfarin who are attempting pregnancy be monitored with frequent pregnancy tests. They recommend substituting UFH or a LMWH for warfarin when pregnancy is achieved. LMWHs cause less HIT and bone loss during pregnancy than UFH.

The pharmacokinetics of LMWH in pregnancy is significantly altered. Consideration should be given to monitoring the anti-Xa activity at 12 to 15 weeks and 30 to 33 weeks.

When possible, patients using UFH or a LMWH should have a planned delivery. UFH should be discontinued 6 hours prior to a planned delivery. LMWH should be discontinued 24 hours prior to a planned delivery.

Evidence supporting this recommendation is of class: R

16. **Breast Feeding**

Heparin is not secreted in breast milk and can be given safely to nursing mothers.

Evidence supporting this recommendation is of class: R

Unfractionated Heparin

17. **Monitoring**

UFH treatment of thrombosis can be monitored using an activated partial thromboplastin time (aPTT) or heparin assay. The recommended test for monitoring UFH, including the therapeutic range for the test, should be provided by the laboratory. Of note, aPTT results vary among institutions due to differences in laboratory instruments and reagents. The aPTT therapeutic range should correspond to a plasma heparin concentration of 0.3 to 0.7 units/mL by an anti-Xa inhibition assay (0.2 to 0.4 units/mL by protamine titration assay).

Heparin assays are being increasingly used for monitoring UFHs in the treatment of venous thromboembolism. The suggested target therapeutic range is 0.35 to 0.7 units/mL by the anti-Xa inhibition assay. Monitoring unfractionated heparin using a heparin assay may be indicated when the expected aPTT prolongation is not observed despite high doses of UFH (greater than 35,000 U unfractionated heparin in 24 hours), when the pretreatment aPTT is prolonged or when a lupus anticoagulant has been previously documented in the patient.

Patients receiving UFH or a LMWH should be monitored for HIT with a platelet count beginning at baseline, then every other day. A platelet count of less than 50% of baseline may indicate the development of HIT.

Note: Patients who have not received heparin within the previous three months are unlikely to develop HIT within the first three days of treatment; however, patients who have received heparin within three months may develop HIT more rapidly. Unfortunately, patients are not always aware that they have received heparin (with surgery, central intravenous catheters, etc.) For the sake of safety and simplicity, the workgroup recommends a platelet count every other day for all patients receiving UFH or a LMWH. See Annotation #14, "Adverse Effects" for more information on adverse effects.

Evidence supporting this recommendation is of classes: B, R

18. **Dosing**

Testing must be completed and results reviewed before initiation of UFH:

Complete blood count (CBC)/platelet count

PT/INR

aPTT

Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

Liver enzymes (ALT, AST, GGT)

Albumin

Weight-based, institution specific nomograms are strongly recommended for patients on therapeutic intravenous UFH. Each institution must develop its own nomograms based upon their unique specific therapeutic ranges. See Appendix E in the original guideline document for an example of a heparin nomogram.

A standard weight-based protocol for heparin administration should not be used for patients receiving parenteral platelet receptor glycoprotein IIb/IIIa antagonist (abciximab or ReoPro®), tirofiban (Aggrastat®), eptifibatide (Integrilin®), and/or thrombolytics (alteplase or Activase®). Treating physicians should refer to the specific agent's package insert or their institution protocols for the specific agent's heparin protocol.

Before administering UFH, the patient's height in centimeters and weight in kilograms and any adverse reactions to drugs or food, including a description of the reaction, should be noted.

Before administering UFH, draw hemoglobin/hematocrit, platelet count, aPTT, and PT.

Initiation of UFH

An initial bolus dose of heparin is recommended followed by IV infusion, with the exception of acute stroke. The use of heparin in patients with acute stroke is evolving. See the NGC summary of the ICSI guideline Diagnosis and Initial Treatment of Ischemic Stroke. Note the time of initial heparin bolus.

After initial IV bolus of heparin, begin maintenance drip per institutional protocols.

Maintenance

Obtain an aPTT level or heparin assay six hours after the initiation of IV heparin drip. Adjust the IV drip according to institutional protocols.

Evidence supporting this recommendation is of classes: A, B

19. **Correction of Supratherapeutic Anticoagulation Caused by UFH**

Protamine sulfate administered by slow IV infusion over 10 minutes reverses the anticoagulation effects of unfractionated heparin.

$$\frac{\text{Bolus dose of UFH (units)}}{100} = \text{protamine dose}$$

$$\frac{\text{Hourly infusion rate of UFH (units)}}{40} = \text{protamine dose}$$

Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension.

Evidence supporting this recommendation is of class: R

20. **Key Patient Educational Components**

Importance of understanding heparin assays, INRs, and target ranges

Know and watch for signs of bleeding

Low Molecular Weight Heparin (LMWH)

21. **Monitoring**

Patients receiving LMWH are at lower risk of developing HIT than patients receiving UFH. The need for platelet count monitoring during LMWH therapy depends on the indication for anticoagulation. Postoperative patients receiving LMWH and medical/obstetrical patients receiving LMWH following at least one dose of UFH (including UFH IV flushes) within the past 100 days infrequently experience HIT. Therefore, a baseline platelet count followed by platelet counts every two to three days is recommended until the LMWH is discontinued or until day 14 of therapy, whichever comes first.

Medical and obstetrical patients receiving only LMWH rarely develop HIT. After a baseline platelet count, routine platelet count monitoring is not required. If there is clinical uncertainty about whether the patient may have received UFH, community standard is to monitor platelet counts monthly.

All patients receiving any form of heparin should be instructed to immediately seek medical attention if signs or symptoms of venous thromboembolism are suspected.

Evidence supporting this recommendation is of class: R

22. **Dosing**

Testing must be completed and results reviewed before initiation of LMWH:

Complete blood count (CBC)/Platelet count

PT/INR

aPTT

Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

Liver enzymes (ALT, AST, GGT)

Albumin

LMWH should not be administered by intramuscular injection.

Therapeutic doses of a LMWH are different from prophylactic doses.

Doses of different LMWHs are not interchangeable.

The anticoagulant effect of LMWH can extend beyond 24 hours after administration.

The dose should be modified for patients with impaired renal function. It may be necessary to monitor the anti-Xa level in these patients. LMWHs are relatively contraindicated in patients with a creatinine clearance less than 30 or who are receiving dialysis. To calculate the estimated creatinine clearance, use the Cockcroft-Gault equation as follows:

In men:

Creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{weight in kg}}{(72 \times \text{serum creatinine})}$$

In women:

Creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{weight in kg} \times 0.85}{(72 \times \text{serum creatinine})}$$

The optimal dose of LMWH has not been established in patients with low body weight (less than 50 kg) (possibly higher than usual dose), obesity (possibly lower than usual dose), or pregnancy (changing dose due to changing creatinine clearance). It may be necessary to monitor the anti-Xa level in these patients.

Evidence supporting this recommendation is of classes: D, R

Refer to Table 3 in the original guideline document for therapeutic dosing of LMWH and Table 4 for prophylactic dosing of LMWH.

23. **Correction of Supratherapeutic Anticoagulation Caused by LMWH**

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supratherapeutic anticoagulation with LMWH. Reversal of LMWH with protamine sulfate is incomplete, with neutralization of 60 to 75% at most. However, protamine should be considered for patients with severe life-threatening bleeding. Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension.

If LMWH has been administered within the last 8 hours:

First dose: 1 mg protamine per 100 anti-Xa units LMWH* administered by slow IV infusion over 10 minutes

Second dose: 0.5 mg protamine per 100 anti-Xa units LMWH* administered by slow IV infusion over 10 minutes

* 1 mg enoxaparin - approximately 100 antifactors Xa units

Smaller doses are needed if the LMWH was administered more than eight hours ago.

Evidence supporting this recommendation is of class: R

24. **Key Patient Education Components**

Over-the-counter and prescription drugs which should not be taken while on LMWH

Importance of understanding heparin assay, INRs, and target ranges

Know and watch for signs of bleeding

Proper technique for injecting LMWH

Restrictions for other conditions including DVT, stroke, or coronary artery disease (CAD). Refer to related ICSI guidelines for more information

Importance of adhering to prescribed regimen

Tables of patient education resources, along with patient and provider-oriented websites, are attached in the Support for Implementation section of the original guideline document.

Synthetic Pentasaccharide (Fondaparinux)

26. **Contraindications**

Active major bleeding including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated

Thrombolytics given within past 24 hours for acute stroke

Renal Failure

Fondaparinux has a long elimination half-life and there is no antidote for reversal; therefore, patients who may require rapid reversal are not candidates for this therapy.

27. **Precautions**

Active or history of recent gastrointestinal ulceration and hemorrhage

Bacterial endocarditis

Bleeding diathesis

Concomitant therapy with agents that inhibit platelets

Congenital or acquired bleeding disorders

Hemorrhagic stroke

Status post brain, spinal, or ophthalmologic surgery

Uncontrolled arterial hypertension

Diabetic retinopathy

28. **Adverse Effects**

Anemia has been reported in some patients receiving fondaparinux. Asymptomatic elevation in AST and ALT associated with an increase in bilirubin can occur in a small percentage of patients.

29. **Pregnancy**

The safety of fondaparinux in pregnant women is unknown. Limited clinical experience suggests that fondaparinux may cross the placental barrier resulting in low but measurable anti-Xa activity in the umbilical cord.

Evidence supporting this recommendation is of class: R

30. **Breast-Feeding**

Animal studies have shown secretion of fondaparinux in breast milk. It is unknown if humans secrete fondaparinux in breast milk.

31. **Monitoring**

The heparin assay (anti-Xa) has been used to monitor effects of fondaparinux; however, in most clinical situations, monitoring may not be necessary. Indications for monitoring of fondaparinux include renal insufficiency (calculated creatinine clearance less than 30), low body weight (less than 50 kg), and obesity. There is limited data on use of fondaparinux in pregnancy.

A platelet count should be obtained prior to the initiation of fondaparinux. Antibodies to fondaparinux rarely interact with platelet factor 4. There is one report of HIT with fondaparinux. Fondaparinux is not recommended for patients with platelets less than 100,000 mm^3 due to the overall increased risk of bleeding.

Fondaparinux may cause transient elevations in serum aminotransferases. This effect is reversible and routine monitoring is not recommended.

Additional information on fondaparinux is included in the NGC summary of the ICSI guideline Venous Thromboembolism Prophylaxis.

32. **Dosing**

Testing must be completed and results reviewed before initiation of fondaparinux:

Complete blood count (CBC)/Platelet count

PT/INR

aPTT

Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

Liver enzymes (ALT, AST, GGT)

Albumin

Therapeutic doses are different than prophylactic dosing.

Fondaparinux is not recommended for patients with platelets less than 100,000 mm^3

The dose of fondaparinux should be modified in patients with renal impairment. Fondaparinux is relatively contraindicated in patients with a creatinine clearance less than 30 mL/min. Fondaparinux should not be used in patients who are receiving dialysis.

Fondaparinux is not recommended for patients weighing less than 50 kg.

The optimal dose of fondaparinux has not been established in patients with obesity (possibly lower than usual dose). It may be necessary to monitor the anti-Xa level in these patients.

There is limited data on use of fondaparinux in pregnancy.

See Table 5 in the original guideline document for information on FDA approval status, indications, and dosing of fondaparinux.

Evidence supporting this recommendation is of classes: A, M

33. **Correction of Supratherapeutic Anticoagulation Caused by Fondaparinux**

    There is no antidote for excessive bleeding due to fondaparinux. Recombinant factor VIIa has shown promise as a possible antidote in studies utilizing healthy volunteers. Enzymes capable of degrading heparin have also been investigated as a future treatment for excessive bleeding due to fondaparinux.

    Evidence supporting this recommendation is of classes: A, D, R, Not Assignable

34. **Key Patient Education Components**

    Importance of understanding fondaparinux and target ranges

    Know and watch for signs of bleeding

    Proper technique for injecting fondaparinux

    Restrictions for other conditions including DVT, stroke, or CAD. Please refer to the related ICSI guidelines for more information.

    Importance to adhering to prescribed regimen

Direct Thrombin Inhibitors

35. **Introduction**

    Direct thrombin inhibitors (DTIs) are a relatively new class of anticoagulant drugs. They exert their anticoagulant effect by directly attaching to and inhibiting both free and fibrin-bound thrombin. Potential advantages of these drugs over UFH are inhibition of fibrin (clot) bound thrombin, a more predictable anticoagulant response, and no effect on platelet factor 4. DTIs are presently approved for use in patients with active HIT and those with a previous history of HIT who require anticoagulation therapy.

It is strongly recommended that consultation with a hematologist or anticoagulation expert is done when using these new anticoagulant drugs because of both drug and disease complexities.

36. **Contraindications**
    - Active major bleeding
    - Hypersensitivity to hirudin

37. **Precautions**
    - Severe hypertension
    - History of recent major surgery
    - History of recent major bleeding
    - History of recent cerebrovascular accident
    - Liver dysfunction (argatroban)
    - Renal dysfunction (lepirudin)
    - Gastrointestinal (GI) ulceration
    - Patients with repeat courses may require more frequent monitoring due to antibody formation (lepirudin)
    - Rare case reports of anaphylaxis with reexposure to lepirudin

38. **Adverse Effects**
    - Hemorrhage
    - Patients with repeat courses may require more frequent monitoring due to antibody formation (lepirudin)

39. **Pregnancy**
    - Unknown

40. **Breast-Feeding**
    - Unknown

Types of Direct Thrombin Inhibitors

Argatroban (Acova®)

This is a small molecular weight reversible inhibitor of the active site of thrombin (univalent). This agent is excreted normally in patients with renal insufficiency, but the dose must be reduced in patients with hepatic failure.

Bivalirudin (Angiomax®)

This is a semisynthetic bivalent inhibitor of thrombin. However, unlike hirudin, bivalirudin produces only transient reversal of thrombin and a shorter half-life. It has minimal renal excretion.

Lepirudin (recombinant hirudin) (Refludan®)

This is a potent specific inhibitor of thrombin that forms a slowly reversible complex with the enzyme by binding to both its active site and an exosite focus (bivalent effect). It is cleared predominantly by the kidneys with a half-life of 40 minutes post IV dose and 120 minutes post subcutaneous dose. It

has almost irreversible binding to thrombin and has been associated with an increased risk of major bleeds in one study.

41. **Monitoring**
    - The aPTT testing is commonly used to monitor DTIs.
    - The ecarin clotting time has been shown to be a **superior test** for monitoring recombinant hirudin therapy. However, these tests are not yet widely available in clinical laboratories.

42. **Dosing**

    Testing must be completed and results reviewed before initiation of direct thrombin inhibitors:

    CBC/platelet count

    PT/INR

    aPTT

    Creatinine

    Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

    Liver enzymes (ALT, AST, GGT)

    Albumin

    - **Argatroban (Acova®)**

      Argatroban has a short half-life (less than 1 hour) and is dosed at 2 micrograms/kg/min with adjustments to maintain aPTT at 1.5 to 3.0 times normal (not to exceed 100s).

    - **Bivalirudin (Angiomax®)**

      Bivalirudin is dosed as a 1.0 mg/kg IV bolus, followed by 2.5 mg/kg/hour for 4 hours, followed by 0.2 mg/kg/hour infusion thereafter.

    - **Lepirudin (recombinant hirudin) (Refludan®)**

      The drug is dosed at 0.4 mg/kg bolus IV, followed by 0.15 mg/kg/hour IV with adjustments to maintain aPTT at 1.5 to 2.5 times the median of the laboratory normal range. This range may not be appropriate if the patient's aPTT is elevated at baseline.

43. **Correction of Supratherapeutic Anticoagulation Caused by DTIs**

The major side effect of DTIs is bleeding. This appears to be more significant with the irreversible inhibitor Lepirudin and less so with the reversible inhibitors. There is no antidote for these medications should bleeding occur, which further supports the use of agents with a short half-life.

Evidence supporting this recommendation is of class: R

44. **Key Patient Education Components**

Importance of understanding aPTT and target ranges

Know and watch for signs of bleeding

Antiplatelet Agents

45. **Introduction**

Platelet involvement with pathologic thrombosis and vascular occlusion in both venous and arterial systems has been a recognized target and challenge for therapeutic intervention. Antiplatelet drugs provide relatively safe and variably efficacious alternatives for reduction of excessive risk in several common clinical conditions, notably cardiac and cerebral atherothrombosis. In modern clinical practice, antiplatelet drugs play a role with other means of risk reduction in both primary and secondary prevention of vascular morbidity, and in selected acute event-management situations. There is substantial basic scientific and clinical trial data available to make rational and selective management decisions for individual patients in all conceivable settings of clinical practice. Even more ongoing clinical trials offer a dynamic evolving knowledge base for mundane therapeutic choices, a moving target of expertise.

Principles:

1. Antithrombotic therapeutic benefit is relative to individual patient morbidity, tolerance, and hemorrhagic risk.
2. In general, individual patient thrombotic risk must exceed 3% per year to realize a clinically meaningful benefit from antiplatelet drugs.

For specific treatment recommendations, please see the related ICSI guidelines.

Oral Agents

- Aspirin
- Clopidogrel
- Dipyridamole

Parenteral Agents

- Platelet glycoprotein IIb/IIIa antagonists

Refer to the original guideline document for information on the mechanism of action of antiplatelet agents.

Antiplatelet Agents – Oral

46. **Contraindications**
    - Major hemorrhage
    - Hypersensitivity to NSAIDs [aspirin]
    - Platelet count less than 50,000
    - Syndrome of asthma, rhinitis, and nasal polyps

47. **Precautions**
    - Patients at risk of increased bleeding from trauma, surgery or other pathological condition (particularly gastrointestinal and intraocular)
    - Alcohol use (three or more drinks/day)
    - Pregnancy (third trimester)
    - Gastrointestinal symptoms, peptic ulcer disease
    - Renal failure
    - Severe hepatic insufficiency
    - Concomitant use of more than one antithrombotic drug

48. **Adverse Effects**

Combination of aspirin and clopidogrel and/or combination with warfarin or other anticoagulant have been shown to increase the risk of major bleeding.

Aspirin

Hemorrhage, with underlying hemostatic defects: uremia, hemophilia, anticoagulation therapy. Hemorrhage, without defects: odds ratio (OR) 1.6 in high-risk patients.

Gastric irritation: dose-related

- No better with coated or buffered tablets.

Influence of concomitant COX-2 inhibitors/NSAIDs

- Withhold NSAIDs for 30 minutes after taking aspirin

Clopidogrel

Thrombotic thrombocytopenic purpura (TTP), sometimes life-threatening, may occur, usually within two weeks of treatment initiation.

Hemorrhage 9%; severe in 1%-2%/year of chronic treatment

Thrombocytopenia

Allergic rash

Diarrhea

Dipyridamole

Systemic vasodilation, with secondary dizziness, syncope, myocardial ischemia

Headache

Hemorrhage is NOT a common problem

Evidence supporting this recommendation is of classes: A, D, M

49. **Pregnancy**

    Third-trimester risks of placental separation and hemorrhage

    Evidence supporting this recommendation is of class: A

50. **Breast-Feeding**

    Clinical experience limited; risks cannot be entirely ruled out.

51. **Monitoring**

    In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding is a concern, monitoring may include:

    - CBC/platelet count
    - Fecal blood testing
    - Template bleeding time test

52. **Dosing**

    Aspirin

    For all clinically important endpoint events, oral doses ranging between 81-325 mg/day are sufficient. Higher doses thought in the past to be required for clinical effects have been shown to be unnecessary, and are undesirable because of dose-related gastric and hemorrhagic side effects.

    Aspirin Resistance

    Some patients at risk, as well as volunteer subjects, have shown variably submaximal responses to aspirin, as assessed by bleeding time and *in vitro* laboratory evaluations of platelet response to ADP (adenosine diphosphate) and other activating agents. Methodologic and statistical issues of sampling, and the functional limitations of available laboratory tests, are likely

explanation for the failure to observe such variable dosing requirements in clinical trials.

The ultimate evidence of aspirin resistance would be occurrence of thrombosis and treatment failure, although the presumption of resistance is confounded by the many other factors promoting thrombogenesis at local tissue sites.

Clopidogrel

Loading dose with 300-600 mg results in more rapid effectiveness, but no scientifically established ideal loading schedule is available. A patient-selective phenomenon of "resistance" has been observed, as with aspirin, but again no reliable laboratory test of antiplatelet effect can be recommended.

When using clopidogrel and aspirin in combination, 81 mg dose of aspirin should be used.

Dipyridamole

Antiplatelet oral dosing as Aggrenox®, containing 200 mg modified-release dipyridamole plus 25 mg aspirin. Standard-release oral dipyridamole is considered to be unreliable due to erratic absorption.

Evidence supporting this recommendation is of class: A

53. **Correction of Supratherapeutic Anticoagulation Caused by Oral Antiplatelet Agents**

    Platelet infusion

54. **Key Patient Education Components**

    Importance of understanding antiplatelet agents and target ranges

    Know and watch for signs of bleeding

    Restrictions for other conditions including DVT, stroke, or CAD. Please refer to related ICSI guidelines for more information

    Importance to adhering to prescribed regimen

Antiplatelet Agents -- Parenteral

55. **Contraindications**
    - Bleeding diathesis or oral anticoagulant use within seven days
    - Cerebrovascular accident (CVA) within two years
    - History of vasculitis
    - Intracranial tumor, arteriovenous malformation or aneurysm
    - Major surgery or trauma
    - Severe uncontrolled hypertension

- Thrombocytopenia
- Active or recent internal bleeding

56. **Precautions**
    - Concomitant administration with thrombolytics, oral anticoagulants, NSAIDs, dipyridamole and other antiplatelet drugs increases the risk of bleeding.
    - A low-dose, weight-adjusted heparin regimen is recommended to minimize the risk of bleeding.
    - Minimize arterial and venous punctures, intramuscular (IM) injections and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs.
    - Arterial sheath should not be removed unless aPTT is 50 seconds or less, OR the activated clotting time is 175 seconds or less, and heparin has been discontinued for at least two hours.
    - Full-dose heparin should be stopped at least two hours before femoral artery sheath removal and adequate hemostasis achieved.
    - Patients should be maintained on adequate bed rest following sheath removal or discontinuation of IIB/IIIA.
    - Thrombocytopenia has been observed; platelet counts should be monitored.

57. **Adverse Effects**

    Major bleeding

    Thrombocytopenia [less than 50,000] 1%-2%, usually asymptomatic

58. **Pregnancy**

    Little information is known and not all platelet glycoprotein antagonist drugs have been studied. All studies to date have been animal studies.

59. **Breast-Feeding**

    Little information is known but it does not appear that parenteral antiplatelet drugs are excreted in breast milk.

60. **Monitoring**

    In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding is a concern, monitoring may include:

    - CBC/platelet count
    - Fecal blood testing
    - Template blood bleeding time test

61. **Dosing**

Abciximab

IV bolus 0.25mg/kg plus 0.125 microgm/kg/min infusion; effective in 80% or more in percutaneous coronary intervention (PCI) subjects

Half-life at 30 minutes; 65% attachment to platelet surface

Peak effects at 2 hours: receptor blockade, aggregation, bleeding time

Recovery over 12 to 48 hours

Tirofiban

IV bolus 0.4 microgm/kg/min x 30 min, then 0.1 microgm/kg/min

Renal clearance issues (less than 30 mL/min)

Eptifibatide

IV bolus 180 microgm/kg, infusion 2 microgm/kg/min

Return to normal variable, usually within one hour of discontinuation of infusion

62. **Correction of Supratherapeutic Anticoagulation Caused by Parenteral Antiplatelet Agents**

Platelet infusion

63. **Key Patient Education Components**

Importance of understanding antiplatelet agents and target ranges.

Know and watch for signs of bleeding.

Restrictions for other conditions including DVT, stroke or CAD. Please refer to related ICSI guidelines for more information.

Importance to adhering to prescribed regimen.

64. **Mechanical Heart Valves in Patients Who Are Pregnant**

Patients with mechanical heart valves who are pregnant or attempting to become pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two patients who were pregnant and had mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and the manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valves patients who are pregnant.

Perioperative Management

65. **Anticoagulation Bridging**

PERIOPERATIVE ANTICOAGULATION		Procedure Bleeding Risk	
		LOW	**HIGH**
Patient Thromboembolic Risk	LOW	Continue Warfarin	Hold Warfarin 4 Days Prior To The Procedure (see Table #6. "Recommended Bridging Schedule," below)
	HIGH	Continue Warfarin	Bridging

Risk of Thrombotic Complications in the Absence of Anticoagulation Therapy

Condition	%Thrombotic Risk (Annualized)
Atrial fibrillation (low risk)	1
Atrial fibrillation (average risk)	5
Atrial fibrillation (high risk)	12
Aortic valve prosthesis (dual-leaflet -- St. Jude)	10-12
Aortic valve prosthesis (single-leaflet -- Bjork-Shiley)	23
Mitral valve prosthesis (dual-leaflet -- St. Jude)	22
Multiple prosthesis (St. Jude)	91

Low Bleeding Risk Procedures

For most dental procedures, a review of the literature has shown that in most cases no change in warfarin is needed. It may be reasonable to allow the patient to "drift" to the low end of their therapeutic INR prior to a dental procedure with a high risk of bleeding.

Local bleeding may be controlled with a variety of techniques including pressure, biting on tea bags, gelatin sponges, and topical thrombin. Other means of local hemostasis control include tranexamic acid mouthwash or epsilon aminocaproic acid packing.

Other examples of procedures with low bleeding risk include skin biopsies and cataract surgery. Patients who have procedures that are of low bleeding risk can be continued on warfarin anticoagulation without interruption.

For gynecologic and orthopedic surgical patients at low risk for bleeding, the warfarin dose may be lowered four to five days before surgery and the surgery performed at a lower INR (INR 1.3-1.5). The warfarin dose can be increased to the previous dose postoperatively.

Low Thromboembolic Risk Patients

Patients with low thromboembolic risk, such as patients with atrial fibrillation without prior cerebrovascular accident or other thromboembolic event, may stop warfarin 4 doses prior to the procedure and resume warfarin the evening of surgery. Low thromboembolic risk patients undergoing procedures that require perioperative UFH or LMWH for VTE prophylaxis should receive the recommended prophylaxis in addition to resumption of warfarin.

High Bleeding Risk Procedures for High Thromboembolic Risk Patients -- Bridging

Table 6: Recommended Bridging Schedule

Please be aware that this schedule is not FDA-approved and there are no randomized controlled trials that have studied the efficacy of this schedule. An individual's history of thromboembolism will assist with the decision-making. In general, plan to skip 4 doses prior to the invasive procedure.

Days Before Procedure	Warfarin	INR	Full Dose** LMWH* or Therapeutic UFH
5 days prior to procedure	Last dose	Check if not done within 2 weeks prior	4-5 days before procedure, start after first missed warfarin dose if at very high risk of thrombosis.
4 days prior to procedure	None	None	4-5 days before procedure, start after first missed warfarin dose if at very high risk of thrombosis.
3 days prior to procedure	None	None	AM and PM dose
2 days prior to procedure	None	None	AM and PM dose
1 day prior to procedure	None	Check INR; if INR greater than 1.5, consider 1-2.5 mg Vitamin K by mouth.	AM dose. If UFH is continuous IV infusion, discontinue five hours before surgery. For p.m. dose – if subcutaneous UFH or LMWH, discontinue dose 12 hours before surgery.
Procedure	Resume at regular dose that evening	None	Start at least 12 hours post procedure -- see Annotation #19 of guideline
1 day after procedure	Regular dose	As indicated -- may be skipped	Restart if hemostasis achieved
2 days after	Regular dose	As indicated	Restart if hemostasis

Days Before Procedure	Warfarin	INR	Full Dose** LMWH* or Therapeutic UFH
procedure			achieved
3 days after procedure	Regular dose	As indicated	Continue until INR greater than minimum acceptable x 2 day
4 days after procedure	Regular dose	Daily until INR greater than 2.0, then as indicated	Discontinue

*If enoxaparin is used as the LMWH, dosing is every 12 hours (a.m. and p.m.). Once a day dosing is used if the LMWH is tinzaparin or dalteparin

** Therapeutic refers to full-dose UFH and LMWH for venous thrombosis and not cardioembolic prevention.

Evidence supporting this recommendation is of classes: D, R

66. **Perioperative Management of Antiplatelet Agents**

Patients receiving anti-platelet agents should have these agents stopped 2 to 10 days prior to a procedure:

- Clopidogrel 7 days prior to surgery
- Aspirin 7-10 days prior to surgery
- Ibuprofen 2 days prior to surgery

Cilostazol (Pletal®) does not appear to prolong bleeding times and has no effect on platelet counts in healthy adults.

67. **Neuraxial Blockade Management (Spinal/Epidural)**

New challenges in the management of the anticoagulated patient undergoing neuraxial blockade have arisen as medical standards for the prevention of perioperative venous thromboembolism were established. Likewise, as more efficacious anticoagulants and antiplatelet agents have been introduced, patient management has become more complex.

Regional anesthesia should be avoided in patients with a history of abnormal bleeding or if taking medications that affect hemostasis (e.g., aspirin, NSAIDs, platelet inhibitors, warfarin).

Bleeding or hematomas within the spinal column may result when a heparin product or fondaparinux is used concurrently with spinal or epidural anesthesia or spinal puncture. The risk for complication increases with placement or removal of catheters in the spinal canal and by traumatic or repeated epidural or spinal puncture. Use of other drugs affecting the blood clotting mechanism such as NSAIDs, platelet inhibitors or other anticoagulants also increases the risk of complication.

General Guidelines:

- All patients who receive neuraxial blockade should be monitored closely for developing back pain or signs and symptoms of spinal cord compression (weakness, saddle numbness, incontinence) after injections, during infusions and after discontinuation of infusions.
- Both insertion and removal of neuraxial catheters are significant events. The timing of those events and the timing of any antithrombotic drugs should be taken into consideration, as well as the pharmacokinetics and pharmacodynamics of the specific drugs used.
- The emergence of new drugs and unexplained clinical scenarios can render any guideline obsolete. Consultation with an anesthesiologist experienced in regional anesthesia is essential for novel situations.
- The American Society of Regional Anesthesia and Pain Medicine (ASRA) has developed extensive, peer-reviewed guidelines for the practice of regional anesthesia in the presence of antithrombotic therapy and can be used for detailed management. These guidelines are available at http:/www.asra.com.

Spinal hematomas after neuraxial blockade are very rare (3 in 850,000 in one study) and therefore are difficult to attribute cause and effect. The FDA has received 43 reports of patients with spinal or epidural hematoma after receiving the LMWH enoxaparin. This has prompted the FDA to ask LMWH manufacturers to include warning labels for this complication.

Evidence supporting this recommendation is of classes: D, R, Not Assignable

Warfarin with Neuraxial Blockade

There is no increased risk of perispinal hematoma in patients receiving warfarin postoperatively. However, the mean time to catheter removal was approximately 36 hours, and the majority of patients did not have an INR above 1.5 at the time of removal.

The ASRA guideline (http://www.asra.com) indicates removal of catheter when INR is less than 1.5 with INR checks perioperatively and daily if the first dose of coumadin was given greater than 24 hours preoperatively.

Heparin with Neuraxial Blockade

In general, the most critical time for risk of perispinal hematoma is with indwelling catheter insertion and removal.

Unfractionated Heparin

Unfractionated heparin for VTE prophylaxis in patients receiving neuraxial blockade does not appear to have significant risk. The ASRA guideline indicates no change in approach to patients receiving UFH. If the patient has received four or more days of UFH preoperatively, he/she should be assessed for heparin-induced thrombocytopenia. Optimally, the insertion of an epidural

catheter occurs after three to four half-lives of the drug has elapsed. Depending on the drug and the renal clearance of the patient, this can be 12 to 24 hours for UFH or LMWH. An epidural catheter should be removed when the anticoagulation effect is at its minimum, approximately two hours before the next scheduled injection.

Anticoagulation therapy may be resumed two hours after the catheter has been removed.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin for VTE prophylaxis in patients receiving neuraxial blockade has some potential issues. In 1997, the U.S. FDA issued a physician advisory for LMWH and risk of spinal hematoma. The agency described 43 U.S. patients who developed perispinal hematoma after receiving the LMWH enoxaparin for VTE prophylaxis. Many of these patients developed permanent neurologic sequelae despite 65% receiving aggressive therapy and laminectomy. The median age of the patients was 78 years, and 78% of the patients were women. The potential risk factors were many, including presence of underlying hemostatic disorder, traumatic needle or catheter insertion, repeated needle insertion attempts or a bloody return in the catheter, catheter insertion or removal in the setting of significant anticoagulation, concurrent use of other antithrombotic agents, use of continuous epidural catheters, anticoagulant dosages and vertebral column abnormalities. There were not large enough patient numbers to develop prevalence data nor establish relative risk for any of the individual risk factors. Therefore, no specific conclusions could be made.

Newer Anticoagulant Drugs

The use of the newer factor Xa inhibitor, fondaparinux, or the thrombin inhibitors related to hirudin, is a relative contraindication to all regional anesthesia. The emergence of other newer anticoagulant drugs requires that each be evaluated with regard to its safety in combination with regional anesthesia. In all such circumstances, consultation with an anesthesiologist experienced in regional anesthesia is recommended.

Antiplatelet Agents with Neuraxial Blockade

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial blockade.

There is no wholly accepted test, including the bleeding time, that will guide antiplatelet therapy. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. These conditions include a history of easy bruisability/excessive bleeding, female gender and increased age.

- NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.
- At this time, there do not seem to be specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring or the timing of neuraxial catheter removal.
- The actual risk of spinal hematoma with clopidogrel and the glycoprotein IIb/IIIa antagonists is unknown. Based on labeling and surgical reviews, the suggested time interval between discontinuation of therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel.
- Platelet glycoprotein IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Glycoprotein IIb/IIIa antagonists are contraindicated within four weeks of surgery. Should one be administered in the postoperative period (following a neuraxial technique), the patient should be carefully monitored neurologically.

The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, unfractionated heparin and LMWH, may increase the risk of bleeding complications. Cyclooxygenase-2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation.

Evidence supporting this recommendation is of classes: B, D, R, Not Assignable

68. **Key Patient Education Components**

If a patient is to receive bridging therapy, the patient or a caregiver must show proficiency in the injection technique and proficiency with adhering to the perioperative schedule.

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Nonrandomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Guideline implementation may help the clinician make risk-benefit treatment decisions regarding anticoagulation therapy and appropriately manage patients on anticoagulation therapy to maximize safety and efficacy.

POTENTIAL HARMS

- The major potential side effect of anticoagulation therapy is bleeding either from supratherapeutic effect or by accentuating the blood loss of patients with an existing source of bleeding.
- The major potential harm of withholding anticoagulation therapy is risk for thrombosis.
- Refer to the "Major Recommendations" field for additional details.
- Refer to Annotation Appendix B of the original guideline document for a list of drugs interacting with warfarin and a description of the mechanism of interaction with warfarin.

CONTRAINDICATIONS

CONTRAINDICATIONS

There are no absolute contraindications to anticoagulant therapy. The decision to treat a patient with anticoagulant drugs takes into account an individual patient's risk for thrombosis if not treated weighed against the risk of bleeding while on anticoagulation therapy.

Refer to Annotations 2, 4, 12, 26, 36, 46, and 55 in the "Major Recommendations" section for relative contraindications to antithrombotic therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. An action group is formed when a topic is selected as an initiative. In addition to the action group goals and measures, each medical group sets specific goals they plan to achieve

in improving patient care based on the particular guideline(s).Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

IMPLEMENTATION TOOLS

Patient Resources
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Aug. 64 p. [118 references]

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Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

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Cardiovascular Steering Committee

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This is the current release of the guideline.

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GUIDELINE AVAILABILITY

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Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Anticoagulation therapy supplement. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2007 Aug. 1 p. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.
- ICSI pocket guidelines. April 2006 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2006. 298 p.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following is available:

- Patient education guide to warfarin therapy. Appendix D: Anticoagulation therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Aug.

Electronic copies: Available in Portable Document Format (PFD) from the Institute for Clinical Systems Improvement (ICSI) Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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